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REVIEW ARTICLE

Guanfacine Extended Release: A New Pharmacological Treatment Option in Europe

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Abstract Children/adolescents with attention-deficit/hyperactivity disorder (ADHD) may have a poor or inadequate response to psychostimulants or be unable to tolerate their side-effects; furthermore, stimulants may be inappropriate because of co-existing conditions. Only one non-stimulant ADHD pharmacotherapy, the noradrenaline transporter inhibitor atomoxetine, is currently approved for use in Europe. We review recent advances in understanding of the pathophysiology of ADHD with a focus on the roles of catecholamine receptors in context of the α2A-adrenergic receptor agonist guanfacine extended release (GXR), a new non-stimulant treatment option in Europe. Neuroimaging studies of children/adolescents with ADHD show impaired brain maturation, and structural and functional anomalies in brain regions and networks. Neurobiological studies in ADHD and medication response patterns support involvement of monoaminergic neurotransmitters (primarily dopamine and noradrenaline). Guanfacine is a selective α2A-adrenergic receptor agonist that has been shown to improve prefrontal cortical cognitive function, including working memory. The hypothesized mode of action of guanfacine centres on direct stimulation of post-synaptic α2A-adrenergic receptors to enhance noradrenaline neurotransmission. Preclinical data suggest that guanfacine also influences dendritic spine growth and maturation. Clinical trials have demonstrated the efficacy of GXR in ADHD, and it is approved as monotherapy or adjunctive therapy to stimulants in Canada and the USA (for children and adolescents). GXR was approved recently in Europe for the treatment of ADHD in children and adolescents for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. GXR may provide particular benefit for children/adolescents who have specific co-morbidities such as chronic tic disorders or oppositional defiant disorder (or oppositional symptoms) that have failed to respond to first-line treatment options.

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Key Points

Psychostimulants and the non-stimulant atomoxetine increase the extracellular availability of dopamine and noradrenaline at the synaptic cleft. Although methylphenidate is generally the first choice medication for children/adolescents with attention deficit/hyperactivity disorder (ADHD) in Europe, stimulants can be unsuitable for some patients.

Guanfacine is a selective α2A-adrenergic receptor agonist that acts directly on α2A-adrenergic receptors to enhance noradrenaline neurotransmission; preliminary evidence suggests that guanfacine also influences dendritic spine plasticity in the prefrontal cortex.

Guanfacine extended-release (GXR) is a new non-stimulant pharmacotherapy for ADHD in Europe for children and adolescents for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. The selective mode of action of GXR may provide particular benefit for children/adolescents who have specific co-morbidities such as chronic tic disorders or oppositional defiant disorder (or oppositional symptoms) that have failed to respond to first-line treatment options.

1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a complex and multifactorial neurodevelopmental disorder [1] that is characterized by age-inappropriate and excessive levels of inattention, hyperactivity and impulsivity [2]. ADHD affects approximately 5 % of children and adolescents worldwide [3, 4] and symptoms persist into adulthood in most cases [5]. The disorder is associated with deficits in executive function [6], including working memory [7], and leads to impairment in a broad range of academic and social activities [2]. Emotional dysregulation is increasingly recognized as a common feature of ADHD, and may manifest as extreme irritability, frustration, reactive aggression and temper outbursts [8, 9]. Common ADHD co-morbidities include oppositional defiant disorder (ODD), conduct disorder and chronic tic disorders including Tourette's syndrome [10, 11].

Although understanding of the pathophysiology of ADHD has improved greatly in the past decade, treatment options are still limited. The management of ADHD comprises non-pharmacological interventions, such as behavioural therapy, and pharmacotherapy [12–14]. The psychostimulants methylphenidate (MPH) and amphetamines were the only available ADHD medications for many years. Stimulants have a good effect size (0.8–1.5) [15, 16], and MPH is generally recommended in Europe as the first choice medication for children/adolescents with ADHD [2, 13]. However, approximately 30 % of children/adolescents with ADHD are unresponsive to a single stimulant medication and approximately 10 % fail to respond to any stimulants [17, 18]. Others are intolerant of the side effects of stimulants [19, 20]. Moreover, stimulants may not be the treatment of choice because of a personal or family history of medical conditions, risks of drug diversion or substance abuse, or parental preference [19, 21, 22].

One non-stimulant pharmacotherapy for ADHD, the noradrenaline transporter inhibitor atomoxetine (ATX), is currently approved for use in Europe. The efficacy of ATX in ADHD is well established [23], but potential clinical limitations include a delayed onset of action [24] and sympathomimetic cardiovascular side effects, which are similar to those of stimulants [25]. An alternative non-stimulant medication, particularly one without sympathomimetic cardiovascular side effects, could provide a useful therapeutic option for children/adolescents with ADHD. Guanfacine extended release (GXR; Intuniv) is approved for the treatment of ADHD as monotherapy or adjunctive therapy to stimulants in Canada and the USA (for children and adolescents, 6–17 years) [26, 27]. GXR was approved recently in Europe as part of a comprehensive programme for the treatment of ADHD in children and adolescents for whom stimulants are not suitable, not tolerated or have been shown to be ineffective [28].

Here we provide an overview of recent advances in our understanding of the pathophysiology of ADHD in the context of GXR. This article is intended to provide a clinical perspective on the neurobiology of ADHD and mode of action of pharmacotherapies. Given the broad scope of this article, a formal systematic literature review was not feasible. Rather, we used our combined clinical experience to develop an up-to-date and practical narrative review providing information on ADHD and pharmacological treatment options, with a focus on clinically relevant recent research findings.

2 Methods of Literature Search

Electronic literature searches via MEDLINE/PubMed were conducted for articles published in English (unlimited by date of publication). Combinations of keywords were used to identify relevant articles, including: 'Attention deficit disorder with hyperactivity', 'ADHD', 'ADD', 'pathophysiology', 'neurobiology', 'neurochemistry', 'imaging', 'alpha 2A agonists', 'guanfacine', 'guanfacine extended

release', 'GXR', 'mechanism', 'psychostimulants', 'methylphenidate', 'amphetamine', 'atomoxetine', 'contraindicated', 'adverse events', 'side effects', 'cardiovascular disease', 'hypertension', 'juvenile hypertension', 'tics', 'Tourette's syndrome', 'conduct disorder', 'oppositional defiant disorder' and 'oppositional symptoms'. The last electronic searches were conducted on 15 July 2015. Meta-analyses, systematic and narrative reviews, and original research articles were included. Criteria for each search were adapted according to the initial number of hits. Formal literature searches were also supplemented with key publications, abstracts and posters that were known to the authors.

3 Pathophysiology of Attention-Deficit/Hyperactivity Disorder (ADHD)

Although involvement of the prefrontal cortex (PFC) in ADHD has long been recognized, ADHD is now considered to be a neurodevelopmental disorder that affects the whole brain. The PFC regulates high-order cognitive functions, including attention, behaviour, planning and emotion through working memory [29]. These executive functions involve extensive neural network connections (Fig. 1) [29]. Recent evidence from systems neuroscience-based studies has demonstrated the importance of circuitry and connectivity involving large-scale neural networks in ADHD [30–32]. Accordingly, our understanding of the pathophysiology of ADHD has changed from a model based on specific regional differences to widespread altered connectivity in the whole brain [33].

3.1 Neuroimaging

Recent advances in neuroimaging have allowed the use of innovative high-resolution computational techniques to identify anatomical and functional anomalies in ADHD. Initial magnetic resonance imaging (MRI) studies in ADHD focused on the morphology of discrete brain regions, whereas more recent investigations have evaluated altered connectivity in large-scale neural networks [32, 34, 35].

Neuroanatomical differences between the brains of individuals with ADHD and healthy controls are well established [33]. Longitudinal and cross-sectional structural neuroimaging data indicate that ADHD is characterized by a global delay in brain maturation [30, 36, 37]. Cerebral, cerebellar, grey and white matter volumes are significantly smaller (2.5–4 %) among children/adolescents with ADHD compared with normal controls [30, 37, 38]. Peak cortical thickness is reached significantly later among children/adolescents with ADHD than normal controls (10.5 vs. 7.5 years; $p < 1.0 \times 10–20$) and the delay is most profound in the lateral PFC (Fig. 2) [36]. A

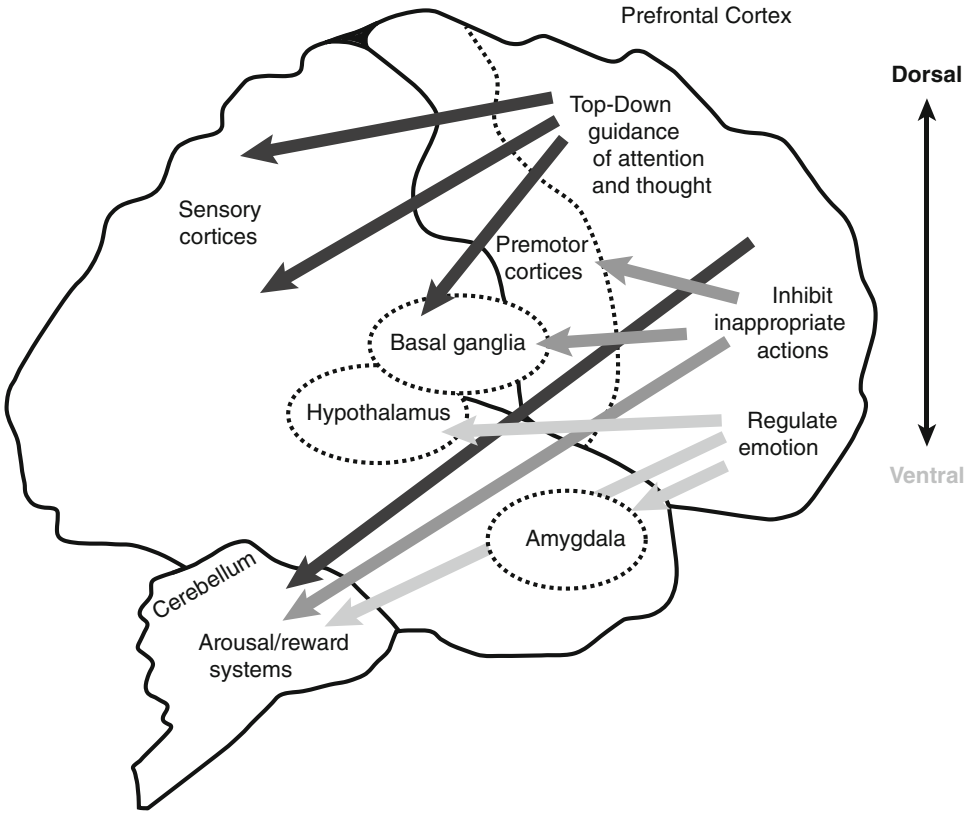

Fig. 1 Regulation of attention, behaviour and emotion through extensive network connections of the prefrontal cortex with other brain regions. Reproduced from Arnsten AF, Rubia K. Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders. J Am Acad Child Adolesc Psychiatry. 2012;51:356–67, © (2012) with permission from Elsevier

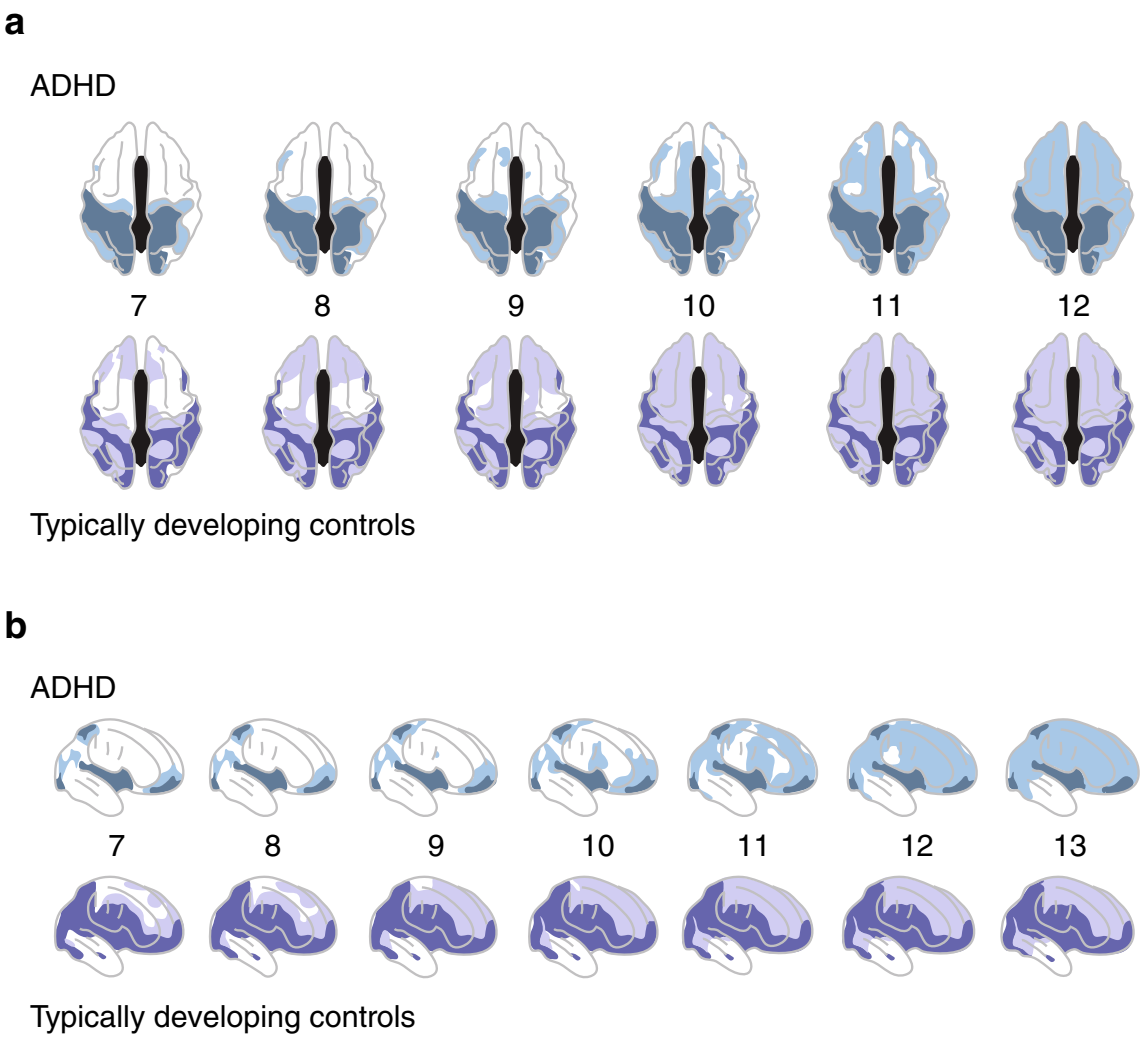

Fig. 2 Attention-deficit/hyperactivity disorder (ADHD) is characterized by a delay in cortical maturation: **a** dorsal view and **b** right lateral view. View of the cortical regions where peak thickness was attained at each age (**a** 7–12 years, **b** 7–13 years) in ADHD (*upper rows*) and typically developing controls (*lower rows*). *Darker colours* indicate regions where a quadratic model was not appropriate (and thus a peak age could not be calculated), or the peak age was estimated to lie outside the age range covered. Both groups showed similar sequences of regions that attained peak thickness, but the ADHD group showed considerable delay in reaching this developmental marker. Reproduced with permission from Shaw et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci USA. 2007;104:19649–54. © (2007) National Academy of Sciences, USA

persistently smaller volume of the superior cerebellar vermis has also been reported in children/adolescents with ADHD versus normal controls, and the development trajectory of the cerebellum may be associated with clinical outcome [39]. Morphological and volumetric changes of subcortical structures, including the thalamus, basal ganglia and limbic system have also been reported [30, 40–42]. The functional significance of these differences in subcortical structures remains unclear but may represent disruption to neural network architecture in ADHD [41].

MRI studies using tractography 3D-modelling techniques have identified altered structural connectivity in white matter tracts among children with ADHD. Diffusion tensor imaging (DTI) provides quantitative data on the integrity of white matter tracts. Reduced volume and integrity of white matter tracts between the thalamus and striatum, hippocampus and PFC have been demonstrated in children with ADHD versus controls [42]. A meta-analysis of data from DTI studies ($n = 15$) suggests that the most consistent alterations in white matter integrity may be found in the right anterior corona radiata, right forceps minor, bilateral internal capsule and left cerebellum [43]. Abnormal connectivity and microstructural integrity in white matter linking the frontal lobe, striatum and cerebellum in children/adolescents with ADHD have also been demonstrated [44]. Moreover, in this study the altered connectivity in some fibre bundles correlated with attentional performance [44].

Network dysfunction in ADHD has been examined systematically using functional neuroimaging. Widespread differences in functional activation between patients with ADHD and normal controls have been described and suggest distinct domain-specific neurofunctional deficits [32, 38, 45]. Functional MRI (fMRI) provides a measure of the activity of neural regions involved at rest or during a particular task [33]. Meta-analyses of fMRI data have shown consistent right fronto-striatal dysfunction during inhibition- and attention-related tasks among patients with ADHD [46]. Attention tasks (data sets $n = 13$) involved the dorsolateral PFC, parietal and cerebellar areas. Inhibition tasks (data sets $n = 21$) involved the inferior frontal cortex, supplementary motor area and anterior cingulate cortex. A further meta-analysis of data from fMRI studies ($n = 11$) showed hypoactivation in the left fronto-parieto-cerebellar areas during timing tasks in ADHD [45].

Recent data indicate that ADHD is associated with dysfunction in large-scale neural networks, including the default-mode network (DMN) [31, 32]. The DMN describes a distinctive set of reciprocally oscillating brain regions that, in normal controls, are active during the resting state and suppressed during goal-directed tasks [47]; in contrast, task-specific neural activity during goal-directed tasks is reduced in patients with ADHD [46]. Resting-state fMRI data have shown dysfunctional connectivity in the DMN in affected children/adolescents and adults versus controls, which supports the hypothesis that ADHD is related to delayed or disrupted maturation of the DMN [31, 32, 35, 48–50]. A comprehensive meta-analysis of fMRI studies ($n = 55$) showed evidence of dysfunction in the DMN and multiple other neuronal systems involved in high-level cognitive functions (executive function and attention) [31]. Moreover, recent data demonstrate altered connectivity in the DMN and other large-scale networks, and structural abnormalities in the dorsolateral PFC and anterior cingulate cortex [32]. Importantly, this modality-spanning study provides evidence of spatial correspondence in the pattern of structural and functional alterations in ADHD [32].

3.2 Neurochemistry

Dysregulated early brain network development (aberrant apoptosis, neurogenesis, neuritogenesis and synaptogenesis) may cause an imbalance in dopamine, noradrenaline and other neurotransmitter systems [51, 52]. Although animal models do not exactly match ADHD, they provide a useful method of studying the molecular pathophysiology of this complex neurodevelopmental disorder [53]. The spontaneously hypertensive rat (SHR) is considered to be the most valid available animal model for ADHD; others, including the Coloboma mouse and actin depolymerizing factor and n-cofilin double mutant mouse models, also provide good approximations. Recent advances in imaging modalities, such as positron emission tomography (PET) and magnetic resonance spectroscopy, have enabled investigation of the neurochemistry of ADHD in humans.

3.2.1 Dopamine and Noradrenaline

Dysregulation of monoaminergic neurotransmitter systems, primarily dopamine and noradrenaline, is hypothesized to play a central role in the pathophysiology of ADHD [33]. Involvement of the dopaminergic system is highlighted by the validity of neonatal 6-hydroxy-dopamine lesioned rats and dopamine transporter (DAT) knockout mice as ADHD models [54]. The SHR model has reduced levels of γ-aminobutyric acid (GABA), which interacts with both the dopaminergic and adrenergic systems in the hippocampus [55]. Alpha2A-adrenergic receptors in the dorsolateral PFC are involved in the regulation of locomotor hyperactivity in primates [56]. Dysregulated dopamine metabolism among treatment-naïve young adults with ADHD has been demonstrated in a PET study using a radiolabelled dopamine precursor [57]. Furthermore, PET imaging of treatment-naïve adult humans with ADHD has shown a reduction in dopamine (D2/D3) receptors in the caudate and limbic system, which correlates with symptoms of inattention [58].

Dopamine and adrenergic receptors are members of the G protein-coupled receptor superfamily of membrane proteins. Dopamine receptors may be classified as either D1 (D1 and D5 subtype) or D2 (D2, D3 and D4 subtype) receptors [59, 60]. Adrenergic receptors mediate physiological responses to adrenaline and noradrenaline. Alpha and β adrenergic receptors are recognized and each has several subtypes [61–63]. α1-Adrenergic receptors are primarily located in smooth muscle, whereas α2-adrenergic receptors are found predominantly in the central nervous system (CNS) and peripheral sympathetic nervous system. Three distinct subtypes of human α2-adrenergic receptors (α2A-, α2B- and α2C-) have been identified [61, 64, 65]. Alpha2B-adrenergic receptors are most prevalent in the thalamus, whereas α2A- and α2C-adrenergic receptors are widespread throughout the brain [66, 67]. The α2A-adrenergic receptor is the most common subtype found in the PFC [68].

In the PFC, α2A-adrenergic and D1 receptors are located predominantly on the dendritic spines of pyramidal neurons [69, 70]. Dendritic spines are tiny protrusions from a neuronal dendrite that interconnect via glutaminergic synapses with other pyramidal neurons in the PFC to form complex neural networks [29]. Noradrenaline and dopamine powerfully modulate network connectivity through their effects on α2A-adrenergic and D1 receptors on dendritic spines [29]. Imbalances in the fine-tuning of pyramidal neurons by noradrenaline and/or dopamine in the

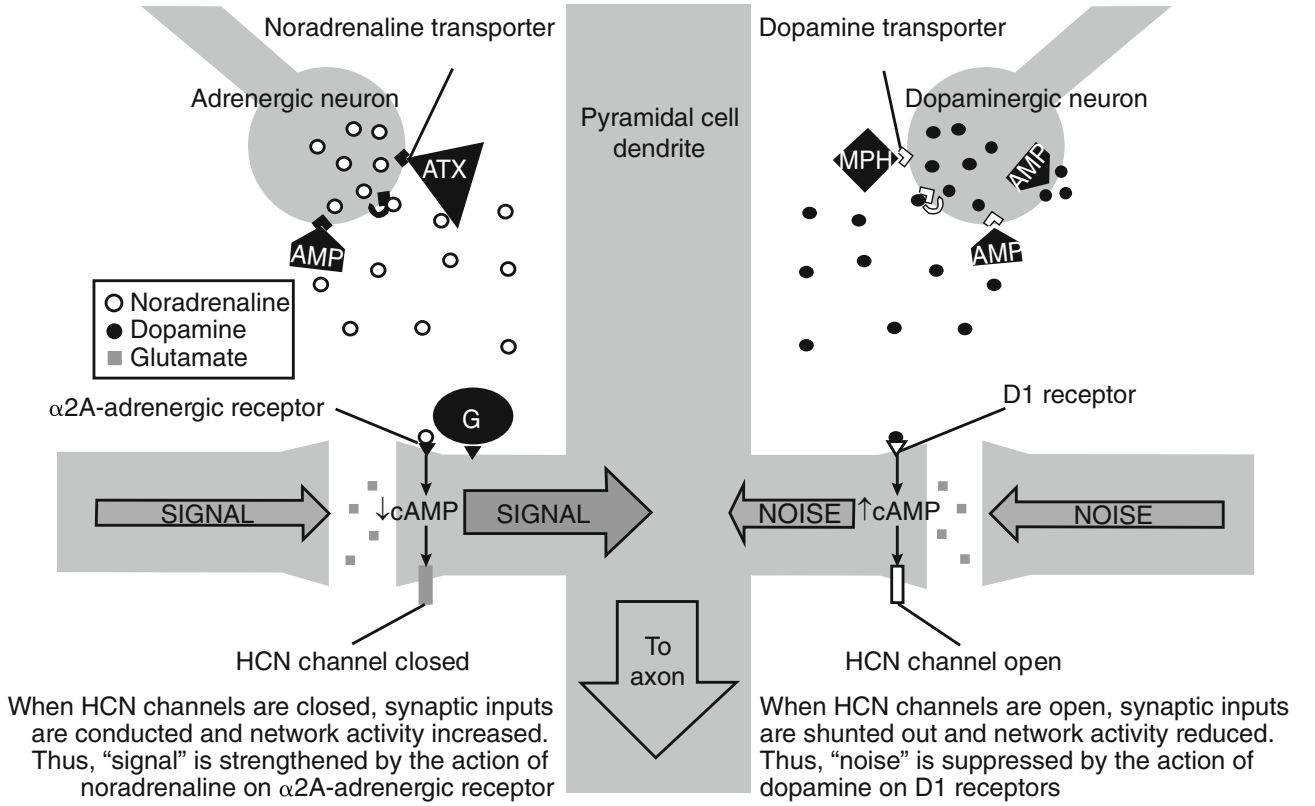

Fig. 3 Noradrenaline and dopamine modulate the strength of network connections at dendritic spines in the prefrontal cortex to influence information processing. Methylphenidate (MPH) primarily blocks the dopamine transporter; amphetamines (AMPs) block the dopamine and noradrenaline transporters, and increase output of dopamine; atomoxetine (ATX) blocks the noradrenaline transporter. Guanfacine (G) directly stimulates postsynaptic α2A-adrenergic receptors and thereby closes hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in the post-synaptic neuron and enhances noradrenaline neurotransmission. Adapted from Wang M et al. Alpha2A-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. Cell. 2007;129:397–410 © (2007) with permission from Elsevier and Arnsten AF, Rubia K. Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders. J Am Acad Child Adolesc Psychiatry. 2012;51:356–67, © (2012) with permission from Elsevier

PFC affect information processing and are believed to underlie the symptoms of ADHD.

Stimulation of D1 receptors by dopamine is believed to increase the production of cyclic adenosine monophosphate (cAMP), thereby opening hyperpolarization-activated cyclic nucleotide-gated (HCN) cation channels near the synapse (Fig. 3) [71]. An open channel causes the signal to 'leak out', thus shunting inputs out of the dendritic spine [72] and weakening network connections [73]. Conversely, stimulation of α2A-adrenergic receptors by noradrenaline inhibits cAMP signalling, thereby closing HCN channels [72]. Closure of the channel allows the signal to be conducted down the pyramidal neuron. In theory, noradrenaline strengthens the appropriate 'signal' between neurons with shared inputs, whereas dopamine reduces 'noise' by dissipating inappropriate network connections [72]. Thus, dopamine and noradrenaline have contrasting but complementary actions to increase the 'signal-to-noise ratio' in the PFC [72].

Moderate stimulation of α2A-adrenergic receptors in the PFC improves working memory in animal models and humans [69, 74, 75]. Similarly, moderate stimulation of D1 receptors in the PFC enhances working memory performance [71]. Both noradrenaline and dopamine concentrations in the synaptic cleft have an 'inverted U-shaped' effect on working memory, in which too much or too little of either neurotransmitter impairs PFC function (Fig. 4) [73]. Excessive levels of noradrenaline at the synapse leads to binding of noradrenaline to other adrenergic receptor subtypes on distant synapses and impairs working memory [73]. Likewise, excessive levels of dopamine may result in the recruitment of other dopamine receptor subtypes [73].

3.2.2 Other Neurotransmitters

ADHD probably results from interplay between several dysfunctional neurotransmitter systems. Another monoaminergic neurotransmitter, serotonin, is postulated

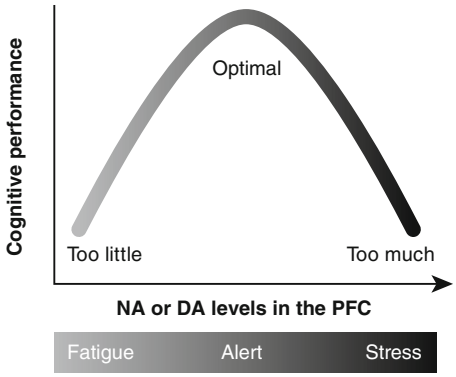

Fig. 4 Inverted U-shaped influence of noradrenaline (NA) and dopamine (DA) on the prefrontal cortex (PFC). Both NA and DA have an 'inverted U-shaped' influence on PFC physiology and cognitive performance; too little or too much of either neurotransmitter impairs PFC function. Adapted with permission from Macmillan Publishers Ltd from Arnsten AF. Stress signalling pathways that impair prefrontal cortex structure and function. Nat Rev Neurosci. 2009;10:410–22

to play a role in ADHD. Paediatric major depressive disorder and paediatric obsessive compulsive disorder share some neuropsychological deficits and affected neural circuits with ADHD [29]. Selective serotonin re-uptake inhibitors are an effective treatment for these two disorders and it has been suggested that they act to normalize serotonergic regulation of emotion and inhibitory control [29]. Moreover, 5HT1B knockout mice exhibit hyperactivity, and attention- and sensation-seeking behaviour [76]. Association studies have identified links between various serotonergic genes and ADHD and there may be a particular association between the serotonin receptor gene, *HTR1B*, and the inattentive subtype of ADHD [77].

Recent evidence suggests that dysfunction in the glutamatergic neurotransmitter system plays a role in the pathophysiology of ADHD [78]. Glutamate is the main excitatory neurotransmitter in the human brain, and a key neuronal growth factor [79]; the glutamate *N*-methyl-D-aspartate (NMDA) receptor NR2 subunit controls synaptic plasticity and memory function during brain development [80]. In vivo data indicate that the glutamatergic system is hyperfunctional in the PFC of the SHR [81]. In addition, increased glutamatergic tone in children with untreated ADHD versus controls [82] and effects on glutamatergic systems following pharmacotherapy have been detected in magnetic resonance spectroscopy studies [83, 84]. Recent data suggest that glutamine levels may be increased among children (but not adults) with ADHD versus controls [85].

Preliminary data suggest that histamine may also be associated with ADHD. Histaminergic pathways are associated with arousal, learning and memory [86–88]. Histamine H3 receptor antagonists improve the performance of the SHR in inhibitory avoidance tasks, thus suggesting a tentative role in the treatment of ADHD [89, 90]. In addition, MPH and ATX are reported to increase histamine release in the PFC of the SHR [89, 91, 92].

3.3 Genetics

The pathophysiology of ADHD has a strong genetic component [93]. Heritability of the disorder is estimated to range from 60 to 80 % [93]. Candidate gene studies have also shown a number of gene variants to be associated with ADHD, including those coding for synaptosomal-associated protein 25 (SNAP-25), dopamine receptors (DRD4) and the DAT (DAT1) [94]. Pooled molecular genetics data support the involvement in genes coding for regulators of synaptic plasticity, including CTNNA2 and KALRN, and cell adhesion molecules in ADHD [95]. However, each gene variant is likely to contribute only a small individual effect [33]. Complex 'gene–gene' and 'gene–environment' interactions may explain how individual genes modify the response to environmental or biological variables [96].

4 Pharmacological Treatment of ADHD

An understanding of the pathophysiology of ADHD and modes of action of pharmacotherapies may help clinicians select the medication with the most appropriate efficacy and safety profile to match the individual needs of each patient [33]. The complex modes of action of ADHD pharmacotherapies are not fully understood. Nonetheless, all empirically effective medications seem to enhance signalling of dopamine and/or noradrenaline in the CNS (Table 1) [72]. The stimulants (MPH and amphetamines) and ATX act indirectly to increase the availability of noradrenaline and dopamine in the synaptic cleft, whereas guanfacine has a direct effect on post-synaptic α2A-adrenergic receptors (Fig. 3).

4.1 α2-Adrenergic Receptor Agonists

Interest in the use of α2-adrenergic receptor agonists for the treatment of ADHD began 30 years ago [97]. Early studies focused on immediate-release clonidine and, later, guanfacine [97, 98]. Clonidine engages equally with all three α2-adrenergic receptor subtypes, and also binds to imidazoline I_1 receptors [98–100]. In contrast, guanfacine has higher affinity for the α2A- than α2B- or α2C-adrenergic receptor subtypes [101, 102]. Indeed, receptor-binding studies have shown guanfacine to be the most selective α2A-adrenergic receptor agonist available [103] and is, thus, referred to as a 'selective' α2A-adrenergic receptor agonist.

Clinical use of immediate-release clonidine and guanfacine is limited by their pharmacokinetic (PK) profiles

Table 1 Summary of the modes of action of stimulant and non-stimulant pharmacotherapies in attention-deficit/hyperactivity disorder (ADHD)

Pharmacotherapy	Mechanism of action
Stimulants	
Amphetamine[a]	Blocks dopamine and noradrenaline transporters and increases output of dopamine
Methylphenidate[a]	Primarily acts by blocking the dopamine transporter to increase dopamine levels
Non-stimulants	
Atomoxetine	Blocks the noradrenaline transporter to moderately increase dopamine and noradrenaline levels
Clonidine[b]	Directly stimulates post-synaptic α2A-adrenergic receptors; also binds to other α2-adrenergic receptor subtypes
Guanfacine[c]	Directly stimulates post-synaptic α2A-adrenergic receptors to enhance noradrenaline neurotransmission

[a] Short- and long-acting formulations are approved for the treatment of ADHD in Europe

[b] Not approved for the treatment of ADHD in Europe

[c] Guanfacine immediate release is not approved for the treatment of ADHD

[98]. Rapid absorption of immediate-release α2-adrenergic receptor agonists leads to high peak plasma concentrations that are associated with side-effects such as sedation and a dry mouth; rapid clearance necessitates frequent dosing through the day [98, 104]. Extended-release formulations of guanfacine and clonidine have been developed to overcome these PK issues. Extended-release clonidine is approved for the treatment of ADHD as monotherapy or adjunctive therapy in children/adolescents in the USA [105]. GXR is approved for the treatment of ADHD as monotherapy or adjunctive therapy in Canada and the USA (for children and adolescents) [26, 27], and was approved recently in Europe as part of a comprehensive programme for the treatment of children and adolescents with ADHD for whom stimulants are not suitable, not tolerated or have been shown to be ineffective [28].

4.1.1 Guanfacine Extended Release (GXR)

Guanfacine directly stimulates postsynaptic α2A-adrenergic receptors to enhance noradrenaline neurotransmission (Fig. 3) [98, 106, 107]. The stimulation of α2A-adrenergic receptors in the PFC produces a beneficial effect on cognitive function. Improvement in attention, working memory and learning with guanfacine has been demonstrated in animal studies [74, 106–115]. A beneficial effect of guanfacine has also been shown on impulsive decision-making behaviour in rats and impulsive self-injurious behaviour in rhesus macaques [116–118]. Moreover, guanfacine (29 μg/kg single dose administered orally) improved spatial working memory and planning in a double-blind, placebo-controlled trial in healthy adults [75]. Guanfacine (1 mg single dose administered orally) has also been shown to modulate emotional biasing of cognitive control in healthy adults [119, 120].

fMRI data show that the effect of guanfacine on emotional biasing of cognitive control in healthy adults is associated with altered functional connectivity between the right and left amygdala and PFC [120]. Preliminary fMRI data suggest that clinical response to GXR (1 mg/day titrated to maximum 4 mg/day) in children/adolescents with ADHD is associated with reduced activation in the right midcingulate and left posterior cingulate cortices [121]. In vivo rat pharmacological MRI data support differing effects of guanfacine in specific areas of the brain [122]; functional blood oxygenation level dependent responses suggest that guanfacine increases neuronal activity in the frontal cortex but decreases activity in the basal ganglia (caudate, putamen and nucleus accumbens) and entorhinal cortex [122].

Three hypotheses, based on in vitro and in vivo animal model data, have been proposed to explain the underlying physiological mechanism of action of guanfacine: (1) the HCN channel and network hypothesis; (2) the excitatory postsynaptic current (EPSC) network hypothesis; and (3) the spinogenic hypothesis.

(1) The HCN channel and network hypothesis provides a short-term mechanism by which α2A-adrenergic receptor agonists may regulate PFC networks. As previously described, stimulation of post-synaptic α2A-adrenergic receptors inhibits the production of cAMP, leading to closure of HCN channels and strengthening of the functional connectivity of PFC microcircuits. Blockade of HCN channels in superficial layers (II/III) of the rat PFC improves working memory performance [69] and guanfacine strengthens delay-related firing of PFC neurons during working memory tasks in electrophysiological primate studies [69].

(2) Stimulation of α2A-adrenergic receptors also suppresses excitatory synaptic inputs in pyramidal neurons [123, 124]. As described above, SHR model data suggest that the glutamatergic system is hyperfunctional in ADHD [81]. The EPSC network hypothesis is derived from in vitro and in vivo studies of rats and suggests that guanfacine may suppress glutamate transmission in deep layers (V–VI)

of the medial PFC via complex intracellular signalling pathways [123, 124].

Further, it has been proposed that the intracellular pathways controlling HCN channels and the suppression of glutamate transmission may be linked [123, 124]. As such, α2A-adrenergic receptor activation may trigger both mechanisms, which work together to fine tune the synaptic inputs of pyramidal cells during different physiological conditions [123, 124]. It is hypothesized that HCN channel control (in layers II/III of the PFC) may predominate at low guanfacine doses, whereas the EPSC network (in layers V–VI) is principally affected at high doses [69, 123]. Indeed, neuronal firing in the PFC during working memory tasks is enhanced by low guanfacine doses and suppressed at high doses [69], whereas EPSC network effects can be demonstrated only at relatively high doses [123]. Thus, guanfacine seems to improve the signal-to-noise ratio in the PFC predominantly through an effect on HCN channels, but may also protect it during extreme stress (when noradrenaline is excessively released) through effects on the EPSC network [123].

(3) The spinogenic hypothesis describes a long-term effect of α2A-adrenergic receptor agonists mediated via dendritic spines. Dendritic spines can change rapidly in shape, volume and number [125, 126]. As previously described, dendritic spine plasticity in the PFC plays a key role in learning and memory [126]. α2A-adrenergic receptor agonists, such as guanfacine, increase the length and density of dendritic spines of cultured mouse cortical neurons [127, 128]. Guanfacine increases the expression of synaptic protein PSD95 and promotes the maturation of dendritic spines of cultured rat cortical neurons [129]. Indeed, recent data show that guanfacine prevents dendritic spine loss in the PFC and protects working memory performance in rats exposed to chronic stress [115].

α2A-Adrenergic receptor agonists also inhibit sympathetic nervous system activity. Guanfacine stimulates postsynaptic α2A-adrenergic receptors in the vasomotor centre of the brainstem to reduce peripheral sympathetic tone, and may also activate peripheral presynaptic α2A-adrenergic receptors [130–132]. Overall, guanfacine acts to decrease heart rate and vascular resistance [133]. Indeed, guanfacine was originally developed as an immediate-release formulation and clinically utilized as a centrally acting antihypertensive agent [134]. Guanfacine is associated with less potent hypotensive and sedative effects than is clonidine [135]. Data from a recent meta-analysis suggest that the relative risk of fatigue and somnolence is higher with extended-release clonidine than GXR as monotherapy for ADHD (10.86 [$p = 0.02$] and 3.21 [$p = 0.0008$], respectively, vs placebo) [136]. The selective affinity of guanfacine for α2A-adrenergic receptors is believed to underlie the differing physiological effects of these two α2A-adrenergic receptor agonists [98]. Detailed description of the pharmacodynamic and pharmacokinetic properties and posology of GXR are beyond the scope of this review, but information is available elsewhere for the interested reader [28, 137, 138].

4.2 Other ADHD Pharmacotherapies

Stimulants (various formulations of short- and long-acting MPH and amphetamines including lisdexamfetamine dimesylate) and ATX are approved for the treatment of ADHD in specific patient populations in many European countries and other regions. Stimulants and ATX act to block the re-uptake of dopamine and/or noradrenaline into the presynaptic neuron. Re-uptake by the presynaptic noradrenaline (norepinephrine) transporter (NET) is the main process by which the effects of noradrenaline are terminated in the CNS [139]. Similarly, dopamine is cleared from the synaptic cleft by re-uptake via the DAT; however, in the PFC, dopamine is also recognized by NETs [140].

Human and primate PET studies indicate that MPH binds predominantly to DATs in the striatum [141, 142]. Accordingly, the therapeutic effect of MPH in ADHD is believed to be primarily due to the blockade of DATs, which increases dopamine levels at the synapse (Fig. 3) [143, 144]. Preliminary data suggest that MPH may also downregulate dopamine turnover in children/adolescents with ADHD [57]. In addition, human PET data suggest that MPH also binds to NETs, but the clinical relevance of this is currently unclear [145]. Effects of MPH on neuronal remodelling in the nucleus accumbens, striatum and other brain regions have also been demonstrated [146–148]. Chronic exposure of mice to MPH increases dendritic spine density [146], and a sustained effect of MPH on synaptic gene and protein expression and synaptic and dendritic spine structure has been shown in rat models [147, 148].

Amphetamines inhibit the re-uptake of dopamine and noradrenaline from the synaptic cleft and induce an efflux of dopamine into the synapse in the PFC, striatum and nucleus accumbens (Fig. 3) [149, 150]. Amphetamines are a competitive substrate for the re-uptake transporters NET and DAT [151]. Inside neurons, amphetamines bind with the vesicular monoamine transporter 2 (VMAT2), thereby preventing the translocation of monoamines into intraneuronal storage vesicles [151]. Amphetamines also weakly inhibit monoamine oxidase (particularly monoamine oxidase A), which reduces intracellular catabolism of neurotransmitters [152]. As the concentration of neurotransmitters in the presynaptic neuron increases, the direction of action of the re-uptake transporter changes direction causing an efflux into the synapse [151].

The non-stimulant ATX inhibits NETs to moderately increase noradrenaline and dopamine levels in the PFC by indirect action (Fig. 3) [153]. ATX is reported to have no effect on dopamine efflux in the striatum or nucleus accumbens [153]. In vitro rodent data suggest that ATX may also block NMDA receptors on cortical and hippocampal neurons, thus affecting glutamatergic transmission [154]. A sustained effect of ATX on synaptic mRNA and proteins involved in neuronal plasticity has been demonstrated in rats [155], and a preliminary report of sustained maintenance of clinical response after discontinuation of long-term ATX warrants further investigation [156]. There seems to be some overlap in the neurophysiological effects of stimulants and ATX. Data from in vitro and in vivo animal studies suggest that both MPH and ATX may indirectly stimulate D1 and α2-adrenergic receptors on post-synaptic neurons in the PFC [157–159]. Human fMRI and arterial spin labelling MRI data also indicate common spatial patterns of brain activity after administration of MPH and ATX [160, 161].

Stimulants are the most widely prescribed class of pharmacotherapy for ADHD but may not be suitable for all children/adolescents [162, 163]. Patients may have a contraindication to MPH or amphetamines, or experience inadequate symptom control or side-effects [17–19, 21]. Common side-effects of stimulant treatment include loss of appetite, weight loss and sleep disturbance [19, 164, 165]. Long-acting formulations of MPH have been developed to allow once-daily dosing. However, long-acting MPH does not provide 24-h coverage [166], so some children/adolescents may experience troublesome symptoms of ADHD during the evening, night or early morning. In addition, recent work has shown that MPH causes chronic changes to pyramidal neuron function and synaptic plasticity in the juvenile rat PFC [167, 168], and the implication of these findings on human neurodevelopment remains unknown. Early PET evidence also suggests that long-term MPH therapy upregulates DATs in the striatum; this could reduce treatment efficacy and lead to ADHD symptom rebound on drug cessation, including during drug holidays [169]. As such, some clinicians may seek alternative treatment options for their patients.

5 Clinical Considerations on GXR

GXR directly stimulates α2A-adrenergic receptors and, according to the HCN channel and network hypotheses, thereby improves the 'signal-to-noise' ratio in the PFC. The selective effects of GXR may translate into clinical benefit for patients who require an alternative pharmacotherapy for ADHD. GXR is readily absorbed after oral ingestion and exhibits a linear PK profile in children and adults [137, 138]. Peak plasma concentration is achieved approximately 5 h after oral administration of a single dose of GXR [137, 170] and it has a long excretion half-life (of approximately 17 h) in adults [137]. Thus, the prolonged-release tablets provide a broad and flat GXR concentration profile [137, 138] that allows once-daily dosing [171]. GXR is bound moderately (70 %) to plasma proteins and metabolized primarily by cytochrome P450 (CYP) 3A4; plasma levels are affected by CYP3A4/5 inducers and inhibitors, such as ketoconazole [26].

5.1 Clinical Data on GXR in ADHD

Clinical trial data show that GXR is effective for the treatment of children and adolescents with ADHD as monotherapy or when administered as adjunctive therapy with stimulants [172–179]. Pivotal trial data on GXR are summarized in Table 2. Once-daily GXR significantly reduces ADHD core symptoms versus placebo among patients aged 6–17 years, and improvement is observed within 2 weeks of starting GXR treatment [173, 176, 177]. A significant improvement in functional outcomes (including Clinical Global Impressions of Improvement scale and Weiss Functional Impairment Rating Scale-Parent Report domains) with GXR was also observed in clinical trials [175, 177, 180]. The effect size of GXR monotherapy on ADHD Rating Scale version IV (ADHD-RS-IV) symptom scores in double-blind, placebo-controlled, pivotal trials ranges from 0.43 to 0.86 (Table 2). This is lower than the effect size of stimulants but similar to that reported for ATX (0.59–0.67) [15, 16, 23]. Head-to-head clinical direct comparison trial data are not available and to our knowledge not currently planned. Indirect comparisons, which must be interpreted cautiously in general, suggest that GXR may confer greater ADHD symptom control than does ATX [177, 181]. However, indirect comparisons should be replicated or supported by direct comparisons before being taken as scientific basis for clinical decision making.

GXR has a broad, smooth and sustained concentration profile (that contrasts with the variable plasma levels associated with long-acting MPH) [137, 138, 166]. Administration of GXR in either the morning or evening is associated with significant and clinically meaningful improvements in ADHD symptoms (Fig. 5) [179]. At least 10–12 weeks of ATX treatment are required to achieve a full response [24]. Data suggest that GXR has a faster onset of efficacy than does ATX (significant placebo-adjusted improvement in ADHD-RS-IV total score observed at Week 1 and Week 3, respectively), although findings should be interpreted cautiously as this study was not designed or powered to compare active treatments [177].

The safety and tolerability of GXR have been well established in clinical trials and post-marketing experience

Table 2 Efficacy data from pivotal trials of GXR

Study design	Primary efficacy endpoint	Key clinical findings (primary endpoint and effect size)
GXR as monotherapy		
A randomized, multi-centre, double-blind, parallel-group, placebo-controlled, fixed-dose escalation study conducted in the USA [173] Children/adolescents (aged 6–17 years) with ADHD ($N = 345$) GXR dose: 2, 3 and 4 mg/day	Change in ADHD-RS-IV total score from baseline to endpoint	Significant reduction in placebo-adjusted LS mean change from baseline in ADHD-RS-IV total scores in all GXR groups: −7.7 ($p = 0.0002$), −7.95 ($p = 0.0001$) and −10.39 ($p < 0.0001$) for the GXR 2, 3 and 4 mg/day groups, respectively GXR effect size: 0.64, 0.66 and 0.86 for the 2, 3 and 4 mg/day groups, respectively (post hoc analysis)
A randomized, double-blind, parallel-group, multi-centre, placebo-controlled, dose-ranging study conducted in the USA [176] Children/adolescents (aged 6–17 years) with ADHD ($N = 324$) GXR dose: 1–4 mg/day	Change in ADHD-RS-IV total score from baseline to endpoint	Significant reduction in placebo-adjusted LS mean change in ADHD-RS-IV total scores in all GXR groups: −6.75 ($p = 0.0041$), −5.41 ($p = 0.0176$), −7.34 ($p = 0.0016$) and −7.88 ($p = 0.0006$) in the GXR 1[a], 2, 3 and 4 mg/day groups, respectively GXR effect size: 0.53, 0.43, 0.58 and 0.62 for the GXR 1[a], 2, 3 and 4 mg/day groups, respectively (post hoc analysis)
A double-blind, randomized, multi-centre, placebo-controlled, dose-optimization study conducted in the USA [179] Children (aged 6–12 years) with ADHD ($N = 340$) GXR dose: 1–4 mg/day (morning or evening dosing)	Change in ADHD-RS-IV total score from baseline to Visit 10 (LOCF)	Significant reduction in LS mean change in ADHD-RS-IV total scores: −20.0, −19.8 and −20.1 for the GXR all active, GXR morning and GXR evening dosing groups, respectively ($p < 0.001$ for all groups vs. placebo) GXR effect size: 0.77, 0.75 and 0.78 for the GXR all active, GXR morning and GXR evening dosing groups, respectively
A study comprising an open-label optimization phase followed by a double-blind, placebo-controlled, multi-centre, randomized withdrawal phase, conducted in the EU, USA and Canada [231] Children/adolescents (aged 6–17 years) with ADHD ($N = 528$) [231] GXR dose: 1–7 mg/day	Proportion of treatment failures[b] [231]	Treatment failure occurred in 49 % of the GXR vs. 65 % of the placebo group ($p = 0.006$) [231] GXR effect size[c] (at end of randomized withdrawal phase): 0.51[d]
A randomized, double-blind, multi-centre, parallel-group, placebo- and active-controlled (ATX reference arm), dose-optimization study conducted in the EU, USA and Canada [177] Children/adolescents (aged 6–17 years) with ADHD ($N = 338$) GXR dose: 0.05–0.12 mg/kg/day	Change in ADHD-RS-IV total score from baseline to Visit 15	Significant reduction in placebo-adjusted LS mean change from baseline in ADHD-RS-IV total score for GXR was −8.9 ($p < 0.001$) GXR effect size: 0.76 (ATX effect size: 0.32)
GXR as adjunctive therapy		
A double-blind, randomized, multi-centre, placebo-controlled, dose-optimization study conducted in the USA [178, 180] Children/adolescents (aged 6–17 years) with ADHD and a suboptimal response to stimulants ($N = 461$) GXR dose: 1–4 mg/day (morning or evening dosing) plus current long-acting, oral stimulant (amphetamine or methylphenidate)	Change in ADHD-RS-IV total score from baseline to endpoint	Significant reduction in placebo-adjusted LS mean change in ADHD-RS-IV total scores in both GXR groups: −4.5 ($p = 0.002$) and −5.3 ($p < 0.001$) GXR morning plus stimulant and GXR evening plus stimulant dosing groups GXR effect size: 0.38 and 0.45 for the GXR morning plus stimulant and GXR evening plus stimulant dosing groups, respectively

ADHD attention-deficit/hyperactivity disorder, *ADHD-RS-IV* ADHD Rating Scale IV, *ATX* atomoxetine, *GXR* guanfacine extended release, *LOCF* last observation carried forward, *LS* least squares

[a] 1 mg dose group weight-restricted to <110 lb

[b] Treatment failure defined as ≥50 % increase in ADHD-RS-IV total score and ≥2 point increase in Clinical Global Impression-Severity score at two consecutive visits vs double-blind randomized withdrawal phase baseline

[c] For the change from baseline in LS mean ADHD-RS-IV total score (secondary endpoint)

[d] Newcorn et al. EPA-0666—long-term maintenance of efficacy of extended-release guanfacine hydrochloride (GXR) in children and adolescents with attention-deficit/hyperactivity disorder (ADHD): double-blind, placebo-controlled, multicentre, phase 3 randomized withdrawal study. Poster presented at 22nd European Congress of Psychiatry, March 2014

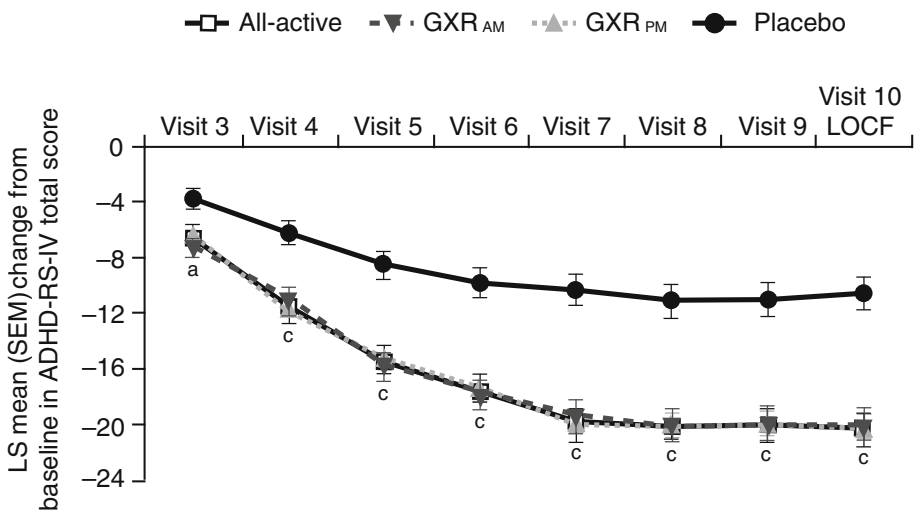

Fig. 5 Guanfacine extended release (GXR) monotherapy administered in either the morning or evening improves attention-deficit hyperactivity disorder (ADHD) symptoms. Mean change from baseline in ADHD Rating Scale version IV (ADHD-RS-IV) total score among patients receiving GXR. *p* values based on type III sum of squares from an analysis of covariance model. [a]$p < 0.05$ vs. placebo based on change from baseline (Visit 2). [c]$p < 0.001$ vs. placebo based on change from baseline (Visit 2). Reproduced with permission from Newcorn et al. Randomized, double-blind trial of guanfacine extended release in children with attention-deficit/hyperactivity disorder: morning or evening administration. J Am Acad Child Adolesc Psychiatry. 2013;52:921–30. © (2013) with permission from Elsevier. *LOCF* last observation carried forward, *LS* least squares, *SEM* standard error of the mean

in Canada and the USA. Treatment with GXR seems to be generally well tolerated [173, 177]. The most frequently reported adverse events associated with GXR in an open-label extension study were somnolence (30.4 %), headache (26.3 %), fatigue (14.2 %) and sedation (13.3 %) [172]. Somnolence/sedation (6 %) and fatigue (2 %) were the most common adverse reactions leading to discontinuation of GXR monotherapy from two large USA studies [173, 176]. Indeed, dose-dependent sedative effects are well described but tend to be transient [172, 173, 175, 182].

GXR is associated with modest dose-dependent reductions in blood pressure and heart rate but hypotension and bradycardia may occur [26, 173, 175]. Cardiovascular effects are reported most frequently in the first month of treatment [172, 173]. Transient hypertension following abrupt discontinuation of GXR has also been reported so the dose should be tapered gradually in decrements of no more than 1 mg every 3–7 days [26, 27]. GXR is associated with QT/QTc prolongation; however, it has a stabilizing effect on cardiac restitution, in line with a lack of arrhythmia liability [183, 184].

GXR is associated with growth that is similar to normative data [26]. ATX carries a black box warning of suicidal ideation [185, 186] but, reassuringly, there are no reports to date of an increased risk of suicide-related behaviour with GXR. Additional information on contraindications, precautions and adverse reactions associated with GXR is available in the Summary of Product Characteristics as reviewed by the European Medicines Agency [28].

5.2 Practical Applications of GXR in ADHD Clinical Practice

Because of its distinct mode of action, GXR may offer a particularly useful alternative treatment option for specific patient populations. The prevalence of ADHD and some commonly co-existing conditions are shown in Table 3. The prevalence of most individual co-morbid conditions among patients with ADHD is relatively low but, when considered together, represents a sizable population with substantial impairment that may be poorly managed using stimulants alone. Clinical efficacy and safety data support the use of GXR among patients with a suboptimal response to stimulants, chronic tic disorders (including Tourette's syndrome) and/or ODD (or oppositional symptoms; Table 4).

5.2.1 Suboptimal Response to Stimulants

GXR is approved for the treatment of ADHD as adjunctive therapy to stimulant medications in Canada and the USA (for children and adolescents). In an open-label trial of children/adolescents with a suboptimal response to long-acting MPH or amphetamine monotherapy, adjunctive GXR was associated with improvement in ADHD symptom scores from baseline (Table 4) [187]. These results were validated in a randomized controlled trial (RCT) of children/adolescents with suboptimal response to long-acting MPH or amphetamines, in which adjunctive GXR significantly improved ADHD symptom scores versus adjunctive placebo (Table 4) [178]. In a recent pre-

Table 3 Prevalence of attention-deficit/hyperactivity disorder (ADHD) and some commonly co-existing conditions for which stimulants are not suitable, not tolerated or have been shown to be ineffective

	Range of prevalence of condition among patients with ADHD	Range of prevalence of ADHD among patients with condition
Stimulants associated with a suboptimal response, contraindicated or potentially unsuitable		
Suboptimal response to stimulant	11–44 % [144, 232–236]	N/A
Intolerant of stimulant side-effects	2–8 % [235, 237]	N/A
Chronic tic disorders (including Tourette's syndrome)	1–33 % [10, 238–246]	11–73 % [241, 243, 244, 247–251]
Cardiovascular disorders (including hypertension and tachycardia)	No data found	70 % in HLHS [252]
Problems relating to emotional regulation and impulse control		
Emotional dysregulation	11–66 % [253–258]	No data found
Oppositional defiant disorder	12–67 % [10, 238–240, 242, 243, 245, 259–264]	30 % [243]
Conduct disorder	5–46 % [10, 238–240, 243, 245, 246, 260–264]	40 % [243]
Addictive behaviour		
Eating disorders	1–16 % [239, 243, 245, 265, 266]	10 % [243]
Substance abuse/dependence	2–16 % [238, 239, 245, 262, 267]	54 % (children) [268]
		18–31 % (adolescents) [268, 269]

HLHS hypoplastic left heart syndrome, *N/A* not applicable

specified subgroup analysis of phase III trial data, GXR monotherapy was associated with a significant improvement in ADHD-RS-IV total scores in both prior-MPH-treated and stimulant-naïve children/adolescents (Table 4), whereas ATX was associated with a significant improvement in ADHD-RS-IV total scores in stimulant-naïve patients only (RCT data only; difference in least squares mean vs. placebo: −5.0 [$p = 0.022$] and −1.8 [$p = 0.452$]) [188]. Appropriately designed randomized studies are needed to confirm the findings of these subgroup analyses and further support treatment sequencing decisions for individuals with ADHD.

5.2.2 *Tics and Related Problems*

Some patients with tic disorders benefit from stimulant medication, as improved concentration can suppress tics; however, others may find that tics are induced or exacerbated [189]. The benefit of α2-adrenergic receptor agonists on both ADHD and co-morbid tic disorders has been demonstrated in a number of studies [190–193]. Guanfacine was effective in reducing tics in two small studies of children with ADHD and co-morbid tic disorders (Table 4) [194, 195]. A systematic review and meta-analysis of data from RCTs ($n = 6$) demonstrated benefit of α2-adrenergic receptor agonists in treating tics among patients with ADHD [196]. At present, the use of GXR/guanfacine for tic disorders in children/adolescents is strongly recommended in Canadian, but not European, treatment guidelines [197, 198].

5.2.3 *Emotional Dysregulation and Oppositional Defiant Disorder (ODD) Problems*

Emotional dysregulation is a common feature of ADHD and is also present in other psychiatric disorders [8, 9]. Dysfunction of a neural network comprising the orbitofrontal cortex, ventral striatum and amygdala is implicated in emotional dysregulation [8]. Guanfacine modulates emotional responses [119] and has been shown to reduce feelings of frustration among children with ADHD [199]. GXR (vs. placebo) significantly reduced oppositional symptoms among children aged 6–12 years with ADHD and co-morbid oppositional symptoms [174], and was associated with significantly greater reduction in oppositional subscale scores than was ATX ($p = 0.01$; Table 4) [200]. Furthermore, adjunctive GXR significantly reduced oppositional symptoms among children/adolescents (aged 6–17 years) with ADHD and oppositional symptoms (Table 4) [201]. It has been postulated that GXR reduces symptoms of aggression by strengthening orbitofrontal cortical regulation of emotion [29]. GXR could offer a useful treatment option for patients with ADHD who experience severe impairment due to emotional dysregulation.

5.2.4 *Intolerable Side Effects of Stimulants*

GXR could hypothetically benefit other specific populations of patients with ADHD, as inferred by its distinct mode of action. This may include patients who experience

Table 4 Specific populations of patients with attention-deficit hyperactivity disorder (ADHD) for whom guanfacine extended release (GXR) or guanfacine immediate release[a] has demonstrated clinical efficacy

Study design	Key findings
Patients with a suboptimal response to stimulants	
An open-label, dose-optimization study of children/adolescents (aged 6–17 years) with a suboptimal response to MPH ($n = 42$) or amphetamine ($n = 33$) [187]	Adjunctive GXR was associated with a significant improvement in ADHD-RS-IV total scores (-16.1, $p < 0.0001$)
A randomized, placebo-controlled trial of children/adolescents (aged 6–17 years) with a suboptimal response to extended-release MPH or amphetamine, who received adjunctive GXR (morning dosing $n = 150$; evening dosing $n = 152$) or adjunctive placebo ($n = 153$) [178]	Adjunctive GXR significantly improved ADHD-RS-IV total scores (placebo-adjusted least squares mean reductions: -4.5 for GXR morning dosing [$p = 0.002$] and -5.3 [$p < 0.001$] for GXR evening dosing)
A pre-specified analysis of data from children/adolescents (aged 6–17 years) in an RCT and the open-label phase of a randomized withdrawal trial [188]	GXR monotherapy was associated with significant improvement in ADHD-RS-IV total scores in both prior-MPH-treated and stimulant-naïve patients (difference in least squares mean vs placebo: -9.8 [$p < 0.001$; $n = 45$] and -7.6 [$p < 0.001$; $n = 60$], respectively, for the RCT and -24.3 [$n = 221$] and -26.7 [$n = 206$], respectively, for the LTE trial [descriptive statistics only])
Patients with chronic tic disorders (including Tourette's syndrome)	
An open-label study of guanfacine immediate release among children (aged 8–16 years) with ADHD and Tourette's syndrome ($n = 10$) [194]	Guanfacine immediate release was associated with improvement in the A task of the Continuous Performance Test (commission errors, $p < 0.02$; omission errors, $p < 0.01$) and the severity of motor and phonic tics (both $p < 0.02$)
A randomized, placebo-controlled trial of guanfacine immediate release among children (aged 7–14 years) with ADHD and tic disorders ($n = 34$) [195]	Guanfacine immediate release improved ADHD-RS total scores (37 vs. 8 %; $p < 0.001$) and Yale Global Tic Severity Scale scores (31 % vs. 0; $p = 0.05$) versus placebo
Patients with oppositional defiant disorder (or oppositional symptoms)	
A randomized, double-blind, placebo-controlled, dose-optimization study of children (aged 6–12 years) with ADHD and oppositional symptoms (GXR, $n = 138$ and placebo, $n = 79$) [174]	GXR significantly improved ADHD-RS-IV total scores and CPRS-R:L oppositional subscale scores compared with placebo (-23.8 vs. -11.5 [$p < 0.001$] and -10.9 vs. -6.8 [$p < 0.001$]). A post hoc analysis showed high correlation between improvement of oppositional and ADHD symptoms ($r = 0.74$) [174]
A matching-adjusted indirect comparison of randomized, double-blind, placebo-controlled trial data to assess the efficacy of GXR ($n = 58$) and ATX ($n = 98$) in reducing oppositional symptoms among children (mean age 10 years) with ADHD and ODD or oppositional/disruptive symptoms [200]	GXR was associated with a greater reduction in mean CPRS-R:S, oppositional subscale scores compared with ATX (-5.0 vs. -2.4; $p = 0.01$)
An assessment of the effect of GXR adjunctive to psychostimulant on oppositional symptoms using data from a multicentre, randomized, double-blind, placebo-controlled, dose-optimization study of children/adolescents (aged 6–17 years) with a suboptimal response to a stimulant alone [201]. Patients received GXR (1–4 mg/day) administered in the morning ($n = 86$) or evening ($n = 93$), or placebo ($n = 95$)	GXR adjunctive to a stimulant significantly improved CPRS–R:L oppositional subscale scores (placebo-adjusted least square mean change from baseline: GXR morning -3.6 [$p = 0.001$] and GXR evening -2.7 [$p = 0.013$]) in a predefined subgroup with oppositional symptoms. A post hoc analysis showed no significant improvement in CPRS–R:L oppositional subscale scores among children/adolescents with a diagnosis of ODD ($n = 90$; although the analysis may have been underpowered to detect a difference between groups)

ADHD-RS-IV ADHD Rating Scale IV, *CPRS-R:L* Conners' Parent Rating Scale-Revised: Long Form, *CPRS-R:S* Conners' Parent Rating Scale-Revised: Short Form, *LTE* long-term efficacy, *MPH* methylphenidate, *ODD* oppositional defiant disorder, *RCT* randomized controlled trial

[a] Guanfacine immediate release is not approved for the treatment of ADHD

intolerable side effects of stimulant medications. Weight loss is a commonly reported side effect of stimulants, and ADHD per se may also be associated with dysregulated growth [202, 203]. Clinicians may prefer to avoid using stimulants among patients with pre-existing low body mass index, as even relatively minor stimulant-related weight reduction may be associated with long-term changes in body composition [204]. In such cases, using, or switching to, a non-stimulant medication can provide a helpful alternative management strategy [205].

5.2.5 Hypertension or Other Cardiovascular Disorders

Juvenile hypertension is being increasingly recognized as an important public health issue [206–208]. Hypertension is estimated to affect up to 6 % of children and adolescents and up to 40 % of those who are overweight or obese [206, 209]. Stimulants and ATX have sympathomimetic effects on the cardiovascular system, including small but significant increases in blood pressure and heart rate [25]. Accordingly, stimulants and ATX are contraindicated for patients with underlying cardiovascular disorders that could be compromised by an increase in blood pressure or heart rate [186, 210]. Thus, a thorough history and examination are required prior to initiation of stimulant treatment to exclude a personal or family history of cardiovascular disorders [2, 186]. GXR does not cause hypertension or affect cardiac re-polarization but may reduce heart rate and blood pressure [131]. Thus, children/adolescents with ADHD and co-existing tachycardia, juvenile hypertension (or prehypertension) or other cardiovascular symptoms could potentially benefit from GXR [189].

5.2.6 Substance Use Disorder and Impulsivity Problems

Children, and adolescents in particular, who have ADHD are impulsive and novelty seeking, and therefore are inherently at higher risk of substance use disorder (SUD) [2, 211]. Unlike stimulants, GXR (and ATX) does not stimulate the nucleus accumbens, which is involved in the regulation of reward-related behaviour [122, 212]. By inference and despite a meta-analysis that demonstrated no association between stimulant use and increased SUD risks [213], GXR could provide a useful additional treatment option for patients who are at particularly high risk of SUD, unable to abstain from substance misuse despite stimulant treatment, or those with family members who are known to misuse drugs. Indeed, guanfacine has been shown to improve resistance to impulsive behaviour in a primate model and human studies [97, 214]. ADHD is a risk factor for children being obese or overweight [215], and dysregulated, impulsive over-eating behaviours are believed to contribute to weight gain [216]. Thus, GXR could theoretically offer a beneficial treatment option for patients with ADHD and associated obesity related to impulsive over-eating.

5.2.7 Circadian Cycle and/or Sleep Problems

The use of GXR to target specific periods of the circadian cycle may be a key application in clinical practice. The early morning routine can be a particularly challenging time of day for families of children with ADHD [217]. Our clinical experience suggests that executive functional deficit resulting in disorganized or oppositional behaviour before the morning dose of ADHD medication is a common and severely disruptive problem. Recent data suggest that GXR administered in the morning may result in a reduced total sleep time versus placebo among children with ADHD and pre-existing sleep problems (−57 vs. +31 min; $p = 0.005$) [218]. The author suggests a possible link between reduced sleep time with GXR and daytime somnolence [218]; however, as this study was terminated early and thus lacks sufficient statistical power, it should be considered as preliminary evidence that needs further investigation. Stimulants in particular may cause sleep disturbances if administered in the evening so should be administered at this time only very cautiously [19, 219], whereas GXR can be administered either in the morning or in the evening [179]. The mode of action of GXR infers that administration in the evening could help children with ADHD to sleep and wake up relatively symptom-free. Indeed, recent data show that morning or evening administration of GXR significantly improves ADHD-related symptoms in the morning and throughout the day (as assessed by modified Connors' Parent Rating Scale–Revised: Short Form total scores; $p < 0.001$ vs. placebo at Week 8 regardless of the time of GXR administration) [220]. GXR administered in the morning or evening adjunctively with a psychostimulant is also associated with improvement in morning symptoms of ADHD [180].

5.3 Other Potential Clinical Applications of GXR

Previous studies also suggest that GXR, through its specific mode of action on the PFC, could offer an effective therapy for conditions other than ADHD. Post-traumatic stress disorder (PTSD) is associated with excessive noradrenaline release [221] and PFC dysfunction may contribute to the inadequate inhibition of traumatic memories [221]. Indeed, there is substantial symptom overlap and co-morbidity between ADHD and PTSD [222]. Rat studies have shown that guanfacine reverses stress-induced PFC deficits while not exacerbating conditioned fear [112, 223]. Moreover, GXR (1–4 mg administered once daily) was found to

reduce the severity of traumatic stress symptoms among children/adolescents in an open-label pilot study [224].

α2A-Adrenergic receptor agonists, including guanfacine, have also been studied in other PFC-associated cognitive disorders. Early data suggest that guanfacine may have beneficial effects in the treatment of attention disorders associated with neurological conditions [225–227]. Improvement with guanfacine has been reported among selected patients who have mild traumatic brain injury, visual neglect following stroke, and deficits in arousal and sustained attention following acute disseminated encephalomyelitis [225–227]. In a rat study, guanfacine has been reported to prevent hypobaric hypoxia-induced spatial working memory deficits and neurodegeneration [228]. The results suggest a potential role for GXR in improving prefrontal cognitive function during high altitude exposure [228].

6 Future Perspectives

Further research into the pathophysiology and aetiological heterogeneity of ADHD and the modes of action of effective pharmacotherapies will increase the use of individualized patient management strategies [229]. The identification of patients with ADHD who are likely to respond to specific treatments and/or avoid side effects using baseline demographic or clinical characteristics (including co-morbidities and adverse reaction profiles) could improve outcomes [230]. Matching individual patients with the most appropriate treatment strategy would help to better address the needs of patients and their families and improve the cost-effectiveness of care [230]. Advances in the neurobiology of ADHD will also help to drive the research and development of new therapeutic options.

7 Conclusions

This article provides an overview of recent advances in neurobiology of ADHD and the mode of action of guanfacine. An understanding of the neurobiology of ADHD and available treatment options will help clinicians make informed decisions to optimize the care of patients who require an alternative pharmacotherapy. ADHD is a neurodevelopmental disorder that affects synaptic transmission and growth factors throughout the brain. Data from neurobiological studies and medication response patterns in clinical trials support a key role for dopamine and noradrenaline in ADHD. Psychostimulants, and the non-stimulant ATX, increase the extracellular availability of these catecholamines at the synaptic cleft. Although stimulants are the most widely prescribed treatment for ADHD, they can be unsuitable for a sizable proportion of patients.

The selective α2A-adrenergic receptor agonist, GXR, is an alternative non-stimulant ADHD pharmacotherapy. According to the HCN channel and network hypotheses, guanfacine acts directly on α2A-adrenergic receptors to enhance noradrenaline neurotransmission. Animal studies also provide preliminary evidence that guanfacine influences dendritic spine plasticity in the PFC. GXR is a new non-stimulant pharmacotherapy for ADHD in Europe for children and adolescents for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. The selective mode of action of GXR may provide particular benefit for children/adolescents who have specific comorbidities such as chronic tic disorders or ODD (or oppositional symptoms) that have failed to respond to first-line treatment options.

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Compliance with Ethical Standards

Conflict of interest MH has received unrestricted grants to conduct Investigator Initiated Trials (IIT) with products of Engelhard Arzneimittel and Medice. He has received speaker honoraria, travel support and served as an advisor for Lilly, Shire, Medice, Novartis, Engelhard Arzneimittel, Actelion, and Lundbeck. He also holds an international patent on Doppler radar to assess ADHD. WC has received research support from Shire, honoraria for lecturing and consultancy for Flynn Pharma, Janssen and Shire, and support for attending meetings from Janssen and Shire. WC was a member of advisory boards for Shire. AL has received unrestricted grants from Medice and Novartis to investigate modes of action of methylphenidate in vitro. She has received speaker honoraria from Shire and Lilly and served as an advisor for Shire.

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